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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,231	01/22/2002	Staffan Nilsson	000510-007	7956
7590	06/13/2005		EXAMINER DEJONG, ERIC S	
Ronald L. Grudziecki BURNS, DOANE, SWECKER & MATHIS, L.L.P. P.O. Box 1404 Alexandria, VA 22313-1404			ART UNIT 1631	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/051,231

Applicant(s)

NILSSON ET AL.

Examiner

Eric S. DeJong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-46 is/are pending in the application.
- 4a) Of the above claim(s) 1-20, 22-28, 32-34, 38 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21, 29-31, 35-37, 39, 40 and 42-46 is/are rejected.
- 7) ☒ Claim(s) 21, 29, 30, and 31 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### **Acknowledgments**

Applicants' response, filed 05/09/2005, containing applicants arguments and an amended set of claims is acknowledged. The new set of claims replaces all previous versions of the claims.

Claims 22 and 32-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Amended claim 22 now recites the limitation of a method for screening nucleation tendency of a molecule in a fluid which is drawn to the non-elected invention of Group I. Claims 32-34 are also drawn to the non-elected invention of Group I due to their dependence from amended claim 22. Applicant timely traversed the restriction (election) requirement in the reply filed on 09/27/2004.

Claims 1-20, 22-28, 32-34, 38, and 41 are withdrawn from consideration. Claims 21, 29-31, 35-37, 39, 40, and 42-46 are currently under examination.

### ***Withdrawal of Previous Claim Objections***

The previous objections to claims 22 and 35 are withdrawn in view of the amendments to made the instant claims, filed on 05/09/2005.

***Claim Objections***

Instant claim 21 is objected as it depends from a withdrawn claim. Claims 29-31 are also included under this objection due to their dependence from claim 21. Appropriate corrections are required. These objections are newly applied.

***Withdrawal of Previous Claim Rejections – 35 USC § 103***

The previous rejection of claims 21, 29-31, 35, 36, 39, 40, and 42-46 under 35 USC §103(a) as being unpatentable over Arnowitz et al. in view of Danley et al. in further view of Schwartz et al. is withdrawn. Upon further consideration, the withdrawal of the rejection is found appropriate as Danley et al. does not fairly disclose the use of a containerless levitating droplet system for use in crystallization procedures.

The previous rejection of claims 21, 29-31, 35-37, 39, 40, and 42-46 under 35 USC §103(a) as being unpatentable over Arnowitz et al. in view of Danley et al. in further view of Schwartz et al. in further view of Schober et al. is withdrawn. Upon further consideration, the withdrawal of the rejection is found appropriate as Danley et al. does not fairly disclose the use of a containerless levitating droplet system for use in crystallization procedures.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21, 29, 30, 35-37, 40, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Schober et al. in further view of Izmailov et al. This rejection is newly applied.

The instant claims are drawn to methods and systems for screening crystallization or amorphous stage conditions of a molecule comprising at least one acoustic levitator for positioning at least one droplet, at least one dispenser for delivering at least one substance that influences nucleation conditions to the positioned

droplet, and one or more means of detecting nucleation tendency in the at least one droplet.

[Claims 21, 29, 30, 35-37, 40, 44, and 45]: Ishikawa et al. set forth the methods and systems for the development of acoustic levitators for containerless protein crystallization (See Ishikawa et al., Abstract), with the cited goal of evaluating the efficacy of levitators in microgravity environments by first assaying the feasibility of such levitators in a 1-g environment as containerless crystallization systems (a method for screening crystallization conditions or amorphous stage conditions for a molecule). Test systems included the employment of a sonic levitator and several 25  $\mu$ l sample droplets of lysozyme protein at various concentrations and salt conditions (at least one levitator for positioning at least one droplet). See Ishikawa et al., page 334, column 1, line 8 through page 335, column 2, line 6. The system employed a charge coupled detector camera (CCD) as a means for detecting and monitoring crystallization conditions in the levitated droplets. See Ishikawa et al., Figure 1. However, Ishikawa et al. discloses that droplets contained an oversaturated sample of lysozyme with variable levels of NaCl, and does not fairly teach delivering at least one substance to the levitating droplet.

Schober et al. taken as a whole teaches using a piezoelectric dispenser for the accurate microdispensation of biochemically relevant solutions and suspensions. Schober et al. also teaches that such piezoelectric devices have been developed and applied in industrial applications, but are well suited for biological sample applications. See Schober et al., page 328, lines 10-19. Further, Schober et al. teaches that manual and mechanical means of dispensing liquids are insufficient for accurate sample

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dispensation of very small volumes, but the disclosed piezoelectric transducer device provides dispensation of very small volumes without any detectable impact on the biological function of dissolved or suspended molecules. See especially Schober et al., Abstract. However, Schober et al. does not fairly teach the delivery of substances from a piezoelectric dispenser to a levitated droplet.

Izmailov et al. sets forth methods and systems for preparing and studying highly supersaturated solutions suspended in a levitator trap. See Izmailov et al., Abstract. Izmailov et al. employ a piezoelectric dispenser to deliver highly accurate volumes of microdroplets to a sample droplet levitated in the center of a spherical void electromagnetic levitator trap (SVELT) in order to investigate homogeneous nucleation conditions. See Izmailov et al., Figure 1 and page 52, column 1, lines 4-53.

Therefore, taken in view of Schober et al. in further view of Izmailov et al., it would have been obvious to one of skill in the art to employ a piezoelectric transducer device to accurately deliver substances to the levitated droplet in the methodology and systems as disclosed by Ishikawa et al. for the optimized development and evaluation of acoustic levitators for containerless protein crystallization.

Claims 31, 42, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Schober et al. in further view of Izmailov et al. as applied to claims 21, 29, 30, 35-37, 40, 44, and 45 above, and further in view of Arnowitz et al.

[Claims 31 and 46]: As presented above, Ishikawa et al. taken in view of Schober et al. taken in further view of Izmailov et al. sets forth the employment of a piezoelectric transducer device to deliver accurate substances to the levitated droplet in conjunction with the methodology and systems as disclosed by Ishikawa et al. in the development of acoustic levitators for containerless protein crystallization. However, neither Izmailov et al, Schober et al., nor Ishikawa et al. fairly teach the crystallization of a nucleic acid, DNA, RNA, an oligonucleotide or a polynucleotide.

Arnowitz et al. sets forth methods and systems for controlling dynamic, reagent induced transformation of multiple biological samples in the optimization of crystallographic conditions. See Arnowitz et al., paragraphs 001 and 0014. Further, Arnowitz et al. discloses that suitable samples for use in the disclosed crystallization methodologies are small and large biomolecules which include macromolecules, proteins, nucleic acids (broadly construed as oligonucleotides and polynucleotides), ligands and drugs. See Arnowitz et al., paragraph 0017.

Therefore, taken in view of Arnowitz et al., it would have been obvious to one of skill in the art to employ the methodology and systems set forth by Ishakawa et al. in view of Izmailov et al. in further view of Schober et al. for the crystallization of nucleic acids, polynucleotides and oligonucleotides.

[Claim 42]: As presented above, Ishikawa et al. in view of Izmailov et al. in further view of Schober et al. sets forth the employment of a piezoelectric transducer device to deliver accurate substances to the levitated droplet in conjunction with the methodology and systems as disclosed by Ishikawa et al. in the development of acoustic levitators for

containerless protein crystallization. However, neither Izmailov et al., Schober et al., nor Ishikawa et al. fairly teach delivery to the at least one levitating droplet by the dispenser a substance that influences nucleation tendency.

Arnowitz et al. sets forth methods and systems for controlling dynamic, reagent induced transformations of multiple biological samples being crystallized. See Arnowitz et al., paragraphs 0001 and 00014. The disclosed supports a deliver system by which multiple reagents effecting nucleation conditions can be delivered to samples that are undergoing crystallization. See Arnowitz et al., paragraph 0072, 0078, and 0082.

Therefore, taken in view of Arnowitz et al., it would have been obvious to one of skill in the art to deliver a substance that effect nucleation conditions to the levitating droplet, as taught by Ishikawa et al. taken in view of Izmailov et al. in further view of Schober et al., in order to enhance the dynamic control of crystallization conditions in a sample.

Claims 39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Izmailov et al. in view of Schober et al. in further view of Arnowitz et al. as applied to claims 21, 29, 30, 31, 35-37, 40, 42, and 44-46 above, and further in view of Schwartz et al.

[Claims 39 and 43]: As presented above, Ishikawa et al. taken in view of Schober et al. taken in further view of Izmailov et al. sets forth the employment of a piezoelectric transducer device to deliver accurate substances to the levitated droplet in conjunction with the methodology and systems as disclosed by Ishikawa et al. in the development of

acoustic levitators for containerless protein crystallization. Further, the levitated droplet as disclosed by Ishakawa et al. is free floating without obstruction from nearly 360°, and thus can be illuminated by light from an illumination source from nearly any direction (broadly construed as the droplet can be illuminated by rotating light). Further, Arnowitz et al. teaches the use of multiple optical sensors for one or more features of light that have traveled through a sample currently undergoing crystallization. However, neither Schober et al., Arnowitz et al., nor Ishikawa et al. fairly teach the detection of nucleation tendency in context of crystal formation by multi-angle light scattering in combination with Raman spectroscopy.

Schwartz et al. teaches the specific use of Raman spectroscopy for monitoring protein concentration to report on nucleation condition of a sample being crystallized. See Schwartz et al., Abstract. Further, Schwartz et al. asserts that Raman spectroscopy is ideal for biochemical experiments in aqueous media (see Schwartz et al., Introduction, final paragraph) and that the disclosed application of the technique greatly enhances the process of determining the necessary criteria for protein crystal growth.

Therefore, taken in view of Schwartz et al., it would have been obvious to one of skill in the art to employ Raman spectroscopy and the sample detection methodologies disclosed by Arnowitz et al. with the methodologies and systems as set forth by Ishikawa et al. taken in view of Schober et al. and Arnowitz et al. in order to enhance the process of determining the necessary criteria for protein crystal growth.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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*John S. Brusca 7 June 2005*  
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